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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,439	04/17/2001	Therese de Bizemont	017753-154	5851

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,439	DE BIZEMONT ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *29 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,3-8 and 10-39* is/are pending in the application.

4a) Of the above claim(s) *13-16,19,22-29 and 31-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,3-8,10-12,17,18,20,21,30 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/17/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10/6/03
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

An amendment was received and entered on 9/29/03. Claims 2 and 9 were canceled as requested.

Claims 1, 3-8, and 10-39 remain pending in the Application.

Claims 13-16, 19, 22-29, and 31-38 were previously withdrawn as being drawn to non-elected inventions.

Claims 1, 3-8, 10-12, 17, 18, 20, 21, 30, and 39 are under consideration in this Office Action.

An Information disclosure statement was received and entered on 10/30/03.

Drawings

The drawings filed with the application are acceptable for examination purposes.

Claim Objections

Claim 1 is objected to because "calls" is misspelled. Substitution of "cells" is suggested.

Claim 6 is objected to because "Watson-Crick's" is misspelled. Substitution with "Watson-Crick" is suggested.

Claim 10 is ungrammatical. The word "is" should be substituted for the word "being", the comma immediately after "phosphodiesterase" should be deleted, and the last instance of "gene" should be pluralized.

Claim 17 is objected to. The final instance of complementary should be deleted and reinserted immediately after "said" and immediately before "part".

Claim 18 is objected to because it contains a typographical error. "66777" should be "677" as in the original claims.

Claim 30 is objected to because it lacks an article immediately preceding the second instance of "eye disease-causing mutation".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3-8, 10-12, 17, 18, 20, 21, and 30 are indefinite because they recite "non-animal or human eye tissue". As far as the Examiner is aware, only animals have eyes. That is, there are no non-animal organisms that have eyes. These claims also recite "non-human" without antecedent basis.

Claims 7, 8, 11, 12, 30, and 39 are indefinite because it is unclear whether the blocks of 2'O-methyl RNA flank only the stretch of DNA, or whether the poly(T) hairpin loops and G-C clamp must be flanked as well. These claims are also indefinite because the metes and bounds of "a stretch" of DNA are unclear. How many bases constitute a stretch? How can one determine what are the metes and bounds of the protection desired by Applicant?

Claims 30 and 39 are confusing because they require a nucleotide or nucleotides invented to revert [sic] eye disease causing mutation. Does Applicant require the invention of a new nucleotide?

Claims 30 and 39 are indefinite because they recite "said at least part" without antecedent basis.

Claim 39 is indefinite because it is unclear if Applicant intends to claim the a pharmaceutical composition comprising the oligonucleotide of claim 30, or whether the claimed oligonucleotide need only contain some portion of the DNA and 2'methoxy RNA of the oligonucleotide of claim 30.

Response to Arguments

Applicant's arguments filed 9/29/03 have been fully considered but they are not persuasive.

Applicant addresses the indefiniteness rejections at pages 32—36 of the response.

Regarding claim 1, Applicant asserts that the claim has been amended to recite non-human animal. This is incorrect. See the claims.

Regarding claims 7, 8, 11, 12, 30, and 39, Applicant argues that the claims are clear because one of skill in the art knows the organization of a chimeric oligonucleotide. This argument is unpersuasive because the issue is not what one of skill in the art knows, but what Applicant's claim recites. The structure recited in the claims is ambiguous for the reasons set forth in the rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1, 3-8, 10-12, 17, 18, 20, 21, 30, and 39 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In ex parte Forman, 230 USPQ 546 (bd. App. 1986) the board considered the issue of enablement in molecular biology and considered several factors. Consideration of these factors in the instant case follows.

Nature of the Invention

The claimed invention is drawn to methods for delivering into target cells of animal tissue in vivo by iontophoresis a chimeric oligonucleotide. In light of the specification and the claims, the recited chimeric oligonucleotides are considered to be chimeraplasts. Chimeraplasts contain a sequence which is largely homologous to a target sequence in the host cell genome, and function to recombine homologously with the target sequence, allowing the introduction of point mutations into the genome. This process is known as chimeraplasty. The invention is asserted to be useful to implement therapy, and to create in vivo disease models. The asserted novelty of the method in general is the use of iontophoresis to improve delivery of chimeraplasts to cells.

Breadth of the Claims

Claims 1-12, 20, and 21 are broadly drawn to methods of introducing chimeric oligonucleotides targeting any gene into "a non-animal or human eye tissue" in vivo or in vitro. For the sake of simplicity the claims have been interpreted as being drawn to human or non-human animal eye tissue. Claims 10, 17, 18, 30, and 39 limit the identity of the target gene. Whereas claims 1, 3-8, 11, 12, 20, and 21 do not. The claims embrace methods of therapy based on the delivery of chimeric oligonucleotides. This is

clear in view of the specification at page 1, lines 12-14 which states that the invention relates to a gene therapy method of treating human eye diseases, and in view of claim 39 which requires that a composition comprising a chimeric oligonucleotide must be enabled for pharmaceutical use.

State of the Art, Predictability of the Art, and Level of Skill of Those in the Art.

The state of the art of chimeraplasty at the time of the invention is set forth by van der Steege et al (Nature Biotechnology 19: 305-306, 4/2001), van der Steege indicates that very few laboratories were able to obtain success using chimeraplasts at the time of the invention. The laboratory of van der Steege, as well as others, persistently failed to reproduce results of another possibly successful laboratory. See e.g. lines 1-10 of paragraph bridging pages 305 and 306. Further, despite obtaining a small degree of apparent success upon visiting this laboratory, van der Steege was subsequently unable to reproduce this result in his own laboratory. Although the prior art comprises scattered examples of apparent success using chimeraplasty, these results were viewed with skepticism prior to and at the time of the invention. Thomas and Capecchi (Science 275(5305): 1404-1405, 1997) noted that one published study indicating a 50-80% mutation rate lacked the proper controls. Stasiak et al (Science 277(5325): 460-462, 1997) concurred with Thomas and Capecchi, and indicated that such results were likely false positives due to artifact or experimental error. Zhang et al (Antisense & Nucl. Acid Drug Dev. 8: 531-536, 1998) attempted to alter nucleic acid sequences using each of 42 different chimeraplast constructs and six different delivery methods, and attempted to perform experiments as closely as possible to those previously published. However, Zhang et al did not achieve a single positive result. Several explanations were posited, including the possibility that the selected target sites were inaccessible, and the possibility that successful application of the method may be

limited by unpredictable factors such as chromatin structure, i.e. histone content or position (see abstract and page 535, column 2, lines 1-18 of last paragraph). Notably, Zhang et al concluded that perceived positive results in the prior art may have been due to PCR artifacts (see paragraph bridging columns 1 and 2 on page 535). Thus at the time of filing, the legitimacy of using chimeraplasts to modify nucleic acid sequences was in doubt, and it was clear that any apparent positive results obtained at that time were not routinely reproducible by those having a high level of skill in the biotechnological art. This is clear evidence of a high level of unpredictability in the art at the time of the invention.

Subsequent to the time of the invention Alberque-Silva et al (Nature Biotechnology 19: 1011, 11/2001) attempted to use chimeraplasty in a variety of experiments, but failed to achieve any significant positive result above background level. Alberque-Silva set forth four criteria for establishing whether or not apparent positive chimeraplasty results are significant, (see four bullets in column 1). Notably, Alberque-Silva indicates that of "the 20 original studies published on chromosomal gene conversion using [chimeraplasty], we found none fulfilling all four of our criteria."

The concerns of Thomas and Capecchi, Stasiak, Zhang, and Alberque-Silva appear to have been well founded in view of a recent review of chimeraplasty (See "The Strange Case of Chimeraplasty, Science (2002) 298:2116-2120). This article indicates that while 9 different laboratories have published apparently successful chimeraplasty studies (see page 2119, column 1, lines 8-12), these results are viewed with skepticism by those of skill in the art, particularly because of the large number of laboratories that have failed to reproduce these results. "*Science* spoke to researchers from over 30 laboratories that had tried [chimeraplasty] and failed to produce evidence that they could target and correct dysfunctional genes, either in vitro or in vivo. Researchers at

biotech companies such as Epoch Biosciences, Isis pharmaceuticals, Millennium Pharmaceuticals, and Lexicon Genetics all failed to get chimeraplasty to work in their labs. Experienced gene-targeting researchers at MITs Whitehead Institute, NIH..., Maine's Jackson Laboratory, and Sweden's Karolinska Institute also saw no effects." (see paragraph bridging columns 1 and 2 on page 2120). "The great majority of researchers interviewed by *Science* say they find the negative results, even though unpublished, more persuasive than the positive ones because they come from independent labs with considerably more experience in gene repair and gene therapy than those that succeeded have." This sentiment is embodied in a quote from Neal Copeland, director of the Mammalian Genetics Laboratory at the National Cancer Institute who said "[t]he people I trusted, the ones who are really good, invested a lot of time, and none of them got it to work." From this it is clear that even those of the highest level of skill in the biotechnological art could not perform chimeraplasty with routine success, and that at best, it must be viewed as a highly unpredictable art. It is important to note that many of these unsuccessful experiments were carried out in vitro using a variety of delivery techniques such as cationic lipid transfection, electroporation, and microinjection, that have proven effective for the delivery of oligonucleotides to cells (See e.g. Zhang (1998), abstract). So, it is highly unlikely that poor oligonucleotide delivery explains the failure of these experiments, and it is equally unlikely that the use of iontophoresis as a delivery technique, as instantly claimed, would have improved the outcome of these experiments.

Guidance and Examples in the Specification

The specification provides no new guidance with respect to the general structural characteristics of chimeraplasts, and the asserted novelty of the invention lies in the use

of iontophoresis to enhance delivery of the oligonucleotides. See e.g. page 6, lines 5-9 of the specification.

The specification teaches a single working example of iontophoresis-mediated chimeraplasty at pages 25-26. A single chimeric oligonucleotide designed to correct a mutation in beta phosphodiesterase was delivered to mouse retinas in vivo by iontophoresis or by subretinal injection. Gene conversion was measured by restriction digest of RT-PCR products. Digestion with BsaI was consistent with gene conversion. Digestion with DdeI was consistent with no conversion. The specification asserts that the results are consistent with gene conversion, however the results appear to be inconclusive for a number of reasons. First, BsaI appeared to digest the control DNA not exposed to the mutagenic chimeraplast. See lanes 17 and 18. Applicant explains this as a lack of specificity already observed in control lane 5. However, if this explanation is accurate, then it is unclear how significant results can be obtained if the restriction enzyme relied upon shows non-specific behavior. Secondly, the prior art and post-filing art teach that PCR-based assays of chimeraplast-driven gene conversion are prone to artifactual results. See Zhang (1998) and Alberque-Silva (2001) above. It is noted that the specification discloses a "highly significant increase in rod-photoreceptor survival" only in chimeraplast/iontophoresis-treated animals, as determined in cell counting assays. However, the results on which this conclusion are based are not presented so an evaluation of the data is not possible. Even if the working example in the specification is significant, and there is substantial reason to doubt that it is, the specification fails to enable the invention as claimed. The prior art teaches that many of those of the highest skill in the art were unable to obtain success with gene conversion even in vitro where it was clear that the oligonucleotides could enter cells. Moreover, those who obtained apparent success with chimeraplasty by performing it in

laboratories that had published successful experiments were unable to reproduce this success upon returning to their own laboratories. See above. The specification has failed to teach how to use the invention to perform gene conversion reproducibly with the unlimited array of chimeraplasts embraced by the broad claims, and it does not present any working example using the chimeraplast recited in the narrowest elected claims, i.e. SEQ ID NO:3. The specification fails to teach what structural chimeraplast features, or technical method steps, will ensure one of skill in the art of achieving reproducible, routine success in the practice of the invention. This is a critical failure in view of the extremely unpredictable state of the art.

It is important to note that although chimeraplasty has been highly unpredictable in terms of reproducibility, the prior art does not identify poor oligonucleotide delivery as an explanation for this problem. Furthermore, it is not clear that iontophoresis results in better delivery of chimeraplasts than do cationic lipid transfection, electroporation, or microinjection. It follows that one of skill in the art would not reasonably expect to improve the predictability of chimeraplasty through the use of iontophoresis as a delivery technique.

Amount of Experimentation Required to Practice the Invention

In view of the uncertain state of the art at the time of the invention, the high level of unpredictability associated with chimeraplasty, the persistent and routine failure of those of skill in the art to obtain positive results using chimeraplasty or to reproduce apparently positive results published in the art, and the failure of the specification to provide substantial additional guidance to that available to those of skill in the art at the time of the invention, one of skill in the art would have had to perform undue experimentation in order to use the invention as intended to effect gene conversion with the broad range of oligonucleotides and in the broad range of tissues contemplated.

Even if Applicant is able to overcome this rejection, the following enablement problems remain.

Claim 5 embraces chimeric oligonucleotides that modify "said target gene in order to modify the expression products of a target gene". This claim establishes no nexus between the "sad target gene" and "a target gene" which has its expression product modified. Broadly interpreted this claim reads on modifying a target gene such that its product becomes involved in posttranslational processing. The specification teaches no examples of this and provides no guidance as to how one of skill in the art should select a mutation to correct that will result in this outcome.

Claim 20 part (K) requires that the donor electrode must be both a needle and a pad electrode. Neither the specification nor the prior art of record teaches such an electrode. US Patent 6,001,088, on which the specification depends for description of this embodiment, teaches that needle and pad electrodes are alternative forms of electrodes, and it does not disclose a combination needle and pad electrode. Therefore in order to practice the invention as claimed, one of skill in the art would have to invent a combination needle and pad electrode. Such experimentation is undue.

Response to Arguments

Applicant's arguments filed 9/29/03 have been fully considered but they are not persuasive.

Applicant addresses the enablement rejection at pages 26-31 of the response.

Applicant makes a series of assertions including:

-the claims as amended now provide clarification to the target genes of interest,

-only one of the references cited by the Examiner as showing the unpredictable state of the art was performed in vivo, whereas the claims are directed to in vivo methods,

-the post filing art (Liang et al (2002) provides guidance regarding optimization of length and structure of RDOs, emphasizing the need for the development of carrier systems.

-Berdugo (2003), Kurz (2002) and Voigt (2002) teach methods of conventional antisense oligonucleotides, or drugs generally, to the eye by iontophoresis, and

-the specification teaches a working example of rod receptor repair using the claimed method.

Applicant's arguments are unpersuasive because, although the rejection clearly established the unpredictability of the art both prior to and after the time the Application was filed, Applicant has provided no evidence or reasoning to show that the specification as filed would have allowed one to predictably and reliably use the claimed invention as intended to revert mutations in the eye in vivo. The Liang reference only confirms the inadequate state of the art at the time of the invention by noting that the delivery techniques, even after the time the invention was filed, were inadequate for the purpose of therapy. Contrary to Applicant's suggestion that Liang made any contribution to the state of the art regarding the length of chimeraplasts, Liang repeats only what was known in the art at the time of filing, i.e. that chimeraplasts are frequently 68 base pairs long. See e.g. page 5753, column 2, first full paragraph. The Berdugo (2003), Kurz (2002) and Voigt (2002) references are not on point because they do not

relate to chimeraplasts. The rejection makes clear that at the time the invention was filed, those of skill in the art were capable of delivering chimeraplasts to target tissue, but were unable to reliably produce the desired mutations. The response provides no evidence that the state of the art at the time of the invention was predictable, that deficiency in chimeraplasty was poor delivery, or that delivery could be improved through the use of iontophoresis. For these reasons the rejection is maintained.

Written Description

Claims 1, 3-7, 11, 12, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3-7, 11, 12, 20, and 21 are drawn to methods of reverting mutations in any gene that is at least partially responsible for an eye disease, As such, practice of the claimed method requires knowledge of the genus of genes that, when mutated, are at least partially responsible for an eye inherited pathology.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species has been described by complete structure, such as nucleotide sequence, next it is determined whether a representative number of species has been described by other relevant identifying characteristic. Applicant is referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The instant specification discloses chimeric oligonucleotides designed to revert mutations in cGMP phosphodiesterase beta subunit, RP1, opsin, and HIF1alpha. Clearly the genus of mutated genes responsible for an inherited pathology is larger than this group. Even the narrower genus of genes that can be partly responsible for an inherited eye pathology is substantially wider than this group,. For example Graeme et al (2002) taught an expressed sequence tag library of adult human lens, and found over 2000 non-redundant transcripts, any of which could conceivably be linked to a heritable disease. The specification describes none of these sequences, nor does it describe by relevant identifying characteristics, i.e. by functional characteristics coupled with a known or disclosed correlation between structure and function, any genes other than cGMP phosphodiesterase beta subunit, RP1, opsin, and HIF1alpha. Further, the specification fails to teach what, if any, combination of structural and functional characteristics these genes have in common that makes them members of the recited genus. As such, the specification fails to describe a representative number of species of a very broad and diverse genuses, and one of skill in the art could not conclude that applicant was in possession of these genuses at the time of the invention.

Response to Arguments

Applicant's arguments filed 9/29/03 have been fully considered but they are not persuasive.

Applicant addresses the written description rejection at pages 31 and 32 of the response.

Applicant asserts that the invention intends to describe a method for targeted gene repair in the eye and retina.

This argument is unpersuasive because it provides no evidence that Applicant was in possession of a representative number of species of the genus of genes involved in eye disease, or more importantly, the particular mutations of these genes that are responsible for disease.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 13-16, 19, 22-29, and 31-38 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441 until 1/13/04, and thereafter will be 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at 703-306-3217 before 2/22/04, and at 571-272-0811 after 2/22/04. The official central fax number is 703-872-9306 until further notice. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413 prior to 1/14/04, and thereafter will be 571-272-0564.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.